

### **REMARKS**

Claims 1, 3, 5, 6, and 8-19 are now pending. Claim 1 has been amended to include further steps in the methodology. No new matter has been added by virtue of this amendment and entry is respectfully requested. Support for the amendments to claim 1 can be found, for example, in Examples 1 and 2. For example, Tables 3 and 4 show the cytokine profile and concentrations of different cytokines in the sample from patients and neutralization results obtained after addition of anti-cytokine agents.

Applicants would also like to thank the Chief Examiner and Examiner Schuberg for the courtesy extended during the teleconference held on July 28, 2008. The teleconference resulted in agreement for Applicants to amend claim 1 to recite a further step directed to identifying the cytokine profile in the sample from patients as compared to normal individuals. The step is followed by addition of an anti-cytokine agent or agents specific for the detected cytokines in the cytokine profile and resulting in the neutralization of the detected cytokines. It was agreed that the amendments should distinguish over the cited references, both in combination and standing alone, as these do not teach or disclose identifying a cytokine profile of each individual patient, followed by contact with a specific anti-cytokine agent such as an antibody or receptor blockers to the cytokines identified in the sample.

Any amendments made by Applicants was solely to respond to the instant Office Action and is not to be construed as surrender of any subject matter. Applicants reserve the right to pursue any amended or canceled subject matter in one or more continuation or divisional applications.

### ***Claim Rejections Under 35 U.S.C. § 103***

Claims 1, 3, 5, 6, and 8-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander *et al* (US 6,180,355 BI) in view of Gruschwitz *et al* (*Journal of Andrology* 1996) and Angelopoulos *et al* (*Fertility and Sterility* 1999) and Brackett *et al*. (*Physical Therapy*, 1996).

Applicants respectfully traverse.

To summarize Applicants' invention, Applicants have discovered that in order to treat infertility in males, especially those with spinal cord injury (SCI) with conditions such as leukocytospermia, a cytokine profile must first be established. As has been discussed in prior responses and the subsequent Declarations filed by Applicants, Applicants have discovered that the presence of different cytokines in the sperm of patients is directly related to decreased sperm motility and as a consequence, infertility. The link between determining a cytokine profile and treating male infertility was discovered by Applicants and has not been taught, suggested or discussed in the literature. The discovery by Applicants, *inter alia*, that there is a variation in the cytokine profile in the sperm of patients and that a cytokine profile should be established prior to any treatment, has not been taught or suggested in the literature and is a unique and novel finding. For example, in some patients TNF $\alpha$  is higher as compared to other cytokines in the cytokine profile. In such cases, the sample from the patient would be treated mainly anti-TNF $\alpha$  antibodies and/or anti-TNF $\alpha$  receptor blockers.

Further, in considering the first of the Graham factors, the scope and content of the prior art does not teach or disclose identifying the presence and concentration of individual cytokines and establishing a cytokine profile in a patient sample, prior to any treatment. Once the profile has been established, then a proper and specific treatment can be initiated to increase sperm motility. As set forth in the Declarations of record, none of the cited art provides a link between a cytokine profile and infertility in patients with SCI, for example. In fact, even Gruschwitz indicates that the art was highly controversial and different studies were finding diametrically opposing results. In order to compact and expedite prosecution, Applicants have amended the claims to recite the step of determining a cytokine profile. None of the references cited discuss, teach or disclose that a cytokine should be established but only discuss generalities which the Examiner's acknowledged during the telephonic interview. For example, Alexander discusses a cornucopia of diseases and cytokines without teaching or disclosing identifying a cytokine profile for use in treating each disease or how to treat such diseases. As Applicants have taught that types and concentrations of cytokines vary between patients, a general methodology and general cocktail of anti-cytokine reagents would not treat male infertility nor would sperm

motility be increased. Alexander further limits any discussion to a systemic treatment which would again have no effect on sperm motility and is in contrast to the instant invention,. Taking Alexander in view of Gruschwitz, Angelopoulos and Brackett do not cure the deficiencies of Alexander. None of these references teach or disclose a cytokine profile, in conjunction with all the steps needed to treat male infertility. Gruschwitz does not teach or disclose a cytokine profile in sperm and thus cannot cure the deficiencies of Alexander. Taking this in view of Angelopoulos to allegedly treat the sperm *in vitro* would still not cure a male of infertility by addition of anti-cytokine agents as the presence of the types and concentrations of cytokines are not identified. Brackett *et al* add nothing further as cytokines were not even discussed in the cited reference.

The second Graham factor requires ascertaining the differences between the art and claims. Applicants have shown in their studies, a cytokine profile should be established. Further, as controls, Applicants have shown that culturing normal sperm with cytokines does not affect the motility of sperm. Alexander does not teach or disclose the treatment of sperm by anti-cytokine agents nor the step of determining a cytokine profile in order to devise a proper treatment protocol. The discussions by Gruschwitz regarding the Examiner's allegations that Alexander can be taken in view of Gruschwitz which allegedly teaches increased levels of cytokines in sperm resulting in decreased sperm motility taken in view of Angelopoulos would not result in one of ordinary skill in the art to arrive at the instant invention. Brackett does not add anything further as there is no teaching as to cytokine production, treatment or identification of a cytokine profile. Thus, the scope of the art does not teach or disclose the instant invention.

Turning to the next Graham factor, the level or ordinary skill in the art, none of the studies have ever linked, taught or disclose the discovery that a cytokine profile should be established, in conjunction with the other disclosed steps in the claims of the instant invention. Indeed, the cited references, standing alone or in combination do not teach or disclose the methods taught by Applicant. Since all of these references have been discussed before Applicants will not repeat them for the sake of brevity.

The last Graham factor considers objective evidence. Applicants have shown that the cytokine profiles between patients vary and in order to provide appropriate treatment, the cytokine profile from each patient should be one of the steps conducted before treatment with anti-cytokine agents. For example, Tables 3 and 4 show the differences in detected cytokines. None of the references standing alone or in combination, teach, suggest or motivate one of skill in the art to identify a cytokine profile, and then add the appropriate anti-cytokine agents to neutralize the cytokines detected and identified in the sperm of patients.

In view of the foregoing, Alexander *et al* in view of Gruschwitz *et al* and Angelopoulos *et al* and Brackett *et al*. to teach or disclose the instant invention. In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant invention.

Claims 1, 3, 5, 6, 8-19 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Skurkovich *et al* (US 5,888,511) in view of Brackett *et al* (*Physical Therapy*, 1996) and Gruschwitz *et al* (*Journal of Andrology*, 1996).

Applicants respectfully traverse.

Applicants have amended claim1 to recite the step of identifying the presence of cytokines and determining the cytokine profile of the patient so that a treatment protocol can be administered which specifically targets the cytokine or cytokines in the patients' cytokine profile. Skurkovich discusses a generalized treatment of autoimmune disease by extracorporeal treatment of bodily fluids over columns with anti-cytokine and anti-TNFR antibodies and returning the fluid of the fluid to a patient. One of ordinary skill in the art would not be motivated to take sperm and pass it over columns and then return it to a patient especially considering the physical attributes of sperm. Furthermore, Skurkovich neither teaches nor discloses obtaining a cytokine profile and determining a specific treatment protocol against the cytokines detected. Brackett *et al* and Gruschwitz fail to cure the deficiencies of Skurkovich as neither of these references teaches the identification of a cytokine profile in the treatment of male infertility.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

### CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections and allowance of the application is respectfully solicited.

If there are any remaining issues or the Examiner believes that a telephone conversation with the undersigned would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

Although, Applicant believes that no further extensions of time are required with submission of this paper beyond the two month extension, Applicant requests that this submission also be considered as a petition for any further extension of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 04-0100.

Respectfully submitted,



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